Complete Summary

GUIDELINE TITLE

Fabry disease in genetic counseling practice: recommendations of the National Society of Genetic Counselors.

BIBLIOGRAPHIC SOURCE(S)

Bennett RL, Hart KA, O'Rourke E, Barranger JA, Johnson J, MacDermot KD, Pastores GM, Steiner RD, Thadhani R. Fabry disease in genetic counseling practice: recommendations of the National Society of Genetic Counselors. J Genet Counsel 2002 Apr;11(2):121-46. [51 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Fabry disease

GUIDELINE CATEGORY

Counseling
Management
Risk Assessment
Screening

CLINICAL SPECIALTY

Cardiology
Dermatology
Family Practice
Gastroenterology
Internal Medicine

Medical Genetics
Nephrology
Neurology
Otolaryngology
Pediatrics
Psychology

INTENDED USERS

Advanced Practice Nurses
Health Care Providers
Nurses
Occupational Therapists
Physician Assistants
Physicians
Social Workers

GUIDELINE OBJECTIVE(S)

To assist health care professionals who provide genetic counseling for individuals and families in whom the diagnosis of Fabry disease is suspected or has been confirmed

TARGET POPULATION

Individuals and families in whom the diagnosis of Fabry disease is suspected or has been confirmed

INTERVENTIONS AND PRACTICES CONSIDERED

1. Assessment, including family medical history and psychosocial history, of the consultand(s)
2. Risk assessment through analysis of the pedigree using principles of X-linked inheritance
3. Offer genetic testing for family members where appropriate including DNA mutation analysis, enzyme analysis for at-risk males and ophthalmologic evaluation, enzyme and DNA mutation analysis for potential carrier females
4. Address psychosocial issues
5. Provide educational services, resources and support
6. Address issues and complications of prenatal diagnosis
7. Provide follow-up including facilitation of additional appointments and referrals to other appropriate professionals
8. Consider ethical and other special issues

MAJOR OUTCOMES CONSIDERED

Not stated

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A literature search for relevant English-language medical articles published between January 1985 and June 2001 was performed using the MEDLINE and PUBMED databases. Bibliographies of articles were also reviewed. Articles were reviewed with particular attention to genetic counseling and diagnostic issues.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The literature was reviewed and evaluated for quality according to the categories outlined by the U.S. Preventive Services Task Force (1995).

I. Evidence obtained from at least one properly designed randomized controlled trial.

II-1. Evidence obtained from well-designed controlled trials without randomization.

II-2. Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

II-3. Evidence obtained from multiple time series, with or without the intervention.

III. The opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not applicable

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The authoring committee sought expert review from specialists in Fabry disease and genetic counseling in the United States. Opinions were sought from representatives of advocacy groups for Fabry disease. The full document was made available for review on the Internet to all Full and Associate members of the National Society of Genetic Counselors (NSGC). At the time, 78% of the 1536 NSGC Full and Associate members were registered on the NSGC listserv. The NSGC Full and Associate membership includes genetic counselors, physicians, nurses, attorneys, PhD genetics professionals, and social workers. The NSGC Ethics Subcommittee (consisting of seven genetic counselors, and an ad hoc bioethicist/clergy representative) and an attorney for the NSGC reviewed the revised document. No conflicts with the NSGC Code of Ethics were identified in the final document. The NSGC Board of Directors approved the final document in August 2001.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Primary Genetic Counseling Considerations: Fabry Disease

Assessment

Ascertain the client´s primary questions and concerns and mutually develop a plan to address these concerns.

Medical Family History

Using standardized pedigree symbols, obtain at least a three generation pedigree from the consultand or proband.

- Targeted medical family history questions are included in Table III of the original guideline document.
- Because Fabry disease is inherited in an X-linked pattern, special attention should be paid to the medical history of maternal relatives of a male proband (i.e., his mother´s siblings and their children, both of her parents and their siblings and children, and the mother´s maternal and paternal grandparents). Family history of maternal relatives of a female proband is also important, as is the history of her father and his relatives.
- Note any consanguinity, documenting the exact relationship of unions between relatives on the pedigree (i.e., consanguinity could put female relatives at risk for being homozygotes).

Verify positive family history with medical records, if possible. Document results of enzyme analysis and/or DNA mutation analysis.

For female carriers, obtain pregnancy history (gravidity, parity, termination of pregnancy, spontaneous abortion), and potential exposure to possible teratogenic agents (See "Teratogenesis," below).

Maintain family history with respect to the confidentiality of the consultand/ proband and extended family members.

Psychosocial History of the Consultand/Proband

Attempt to build a relationship with the consultand/proband by validating, empathizing, and listening. Assess, record, and address the consultand´s/proband´s:

- Level of comprehension and communication
- Level of education, employment, and social functioning, as appropriate
- History of depression (e.g., disturbance in sleep pattern, anxiety, changes in appetite, weight gain or weight loss, fatigue, feelings of hopelessness, loss of libido, suicidal ideation)
- History of alcohol or other drug use (especially a history of using alcohol or other drugs to self-medicate for depression and/or pain control)
- Perceived burden of Fabry disease
- Perceived notions of Fabry disease occurrence/recurrence risks
- Coping skills
- Family and community support systems

Risk Assessment

Analyze the pedigree. Using principles of X-linked recessive inheritance, provide genetic risk assessment for carrier status and the chance of having affected offspring.

- All daughters of an affected male are obligate gene carriers, whereas none of the affected male´s sons will have Fabry disease. If there is consanguinity, females are also potentially at risk for homozygosity.
- Sons of female carriers have a 50% risk of inheriting Fabry disease, and daughters of female carriers have a 50% risk of being carriers.
- Females can have manifestations of Fabry disease because of skewed X-inactivation.

Offer genetic testing for family members, as appropriate (see Figure 2 in the original guideline document).

- Offer DNA mutation analysis for diagnostic or carrier testing if the mutation is known in affected family member(s)
- Offer enzyme analysis for at-risk males
- Offer ophthalmologic evaluation, enzyme and DNA mutation analysis for potential carrier females

Psychosocial Issues

The rate of depression, alcoholism, marital problems, unemployment, and suicide is high among men with Fabry disease. A cohort study of 46 men with Fabry disease found that only 57% were currently employed and 17% had never had a job because of the diagnosis of Fabry disease.

Assess/identify family, peer, and community resources for appropriate services and/or support, and consider referrals as needed.

Assess support services and accommodations in settings for school and/or employment, particularly because rapid changes in environmental temperature and humidity, physical exertion, emotional stress, and fatigue can exacerbate painful crises.

Address psychological issues related to genetic diagnosis such as denial, anxiety, anger, grief, survivor and parental guilt, blame, depression, isolation, inability to cope, hopelessness, damage to self-esteem, changed relationship with family of origin, and change in sense of identity, as indicated.

For an individual affected with Fabry disease, explore the client´s notions of sexuality. The angiokeratomas may be a significant source of embarrassment and psychological stress. A patient in a study at the National Institute of Health summarized his distress by stating, "I have angiokeratomas on my genitalia. When you are planning to lose your virginity, the last thing you want is something that looks like a venereal disease." A significant proportion of individuals with angiokeratomas feared initiating sexual relationships. Chronic pain and fatigue may also contribute to sexual difficulties.

Assess patient´s and family´s preconceived notion of affected or carrier status. Family members may have an incorrect understanding of the inheritance, and therefore they may not be aware of their chances to have a child with Fabry disease. An individual with diagnostic results that are opposite of his or her

preconceived affected status may be at higher risk for adverse psychological consequences.

For individuals/couples at risk to have a child with Fabry disease, assess their feelings about childbearing, prenatal diagnosis, and subsequent options (e.g., pregnancy termination or continuation upon diagnosis of an affected male fetus, feelings about termination of pregnancy given potential treatment options). Assess self-concept as it relates to threatened parental role.

Individuals diagnosed with Fabry disease may have seen many healthcare professionals before receiving a confirmative diagnosis. The average time to diagnosis is 10 years, with affected individuals typically seeing 10 specialists before diagnosis. There may be an inherent distrust of health professionals because of this experience.

Address psychological issues arising from the uncertainty of the variable clinical phenotype.

Individuals with a tentative diagnosis of Fabry disease who are subsequently found to not have this condition may have mixed feelings on receipt of a normal (negative) genetic test result. For example, siblings of individuals diagnosed with Fabry disease may have always thought they would develop the condition, and they may take some time to absorb the information that they are unaffected. The "sick role" may have been unconsciously "assigned" to the family member (preselection) thereby creating the illusion of control over the randomness of gene transmission. Unaffected siblings may also experience survivor guilt.

Make referrals for further psychological counseling as necessary.

Prenatal Diagnosis

Prenatal diagnosis for determining fetal sex is the first step in prenatal diagnosis for Fabry disease. The inability to predict clinical outcome in carrier females, many of whom remain asymptomatic, complicates prenatal counseling and diagnosis. Because of this, prenatal diagnosis for female fetuses is usually not available from the laboratories offering testing. For male fetuses at-risk for Fabry disease, subsequent enzyme analysis, or DNA mutation analysis (if the mutation has been identified in the family) can be performed on chorionic villi (chorionic villus sampling [CVS]) or cultured amniocytes.

If the family mutation is known, preimplantation diagnosis is feasible.

Education/Health Promotion

Discuss the clinical manifestations of Fabry disease in males, and the possibility that females can be affected.

Discuss follow-up recommendations (e.g., identification and testing of at-risk family members, scheduling follow-up visits).

Discuss the genetics of Fabry disease and the approach to testing.

- Review X-linked inheritance and recurrence risks
- Review reproductive options and testing (e.g., adoption, donor egg or donor sperm, prenatal diagnosis); include ethical concerns raised by such options, if appropriate
- Review costs of genetic testing, and test limitations (e.g., enzyme assay can be normal in carrier females; the percentage of residual alpha-gal-A enzyme activity does not correlate with clinical severity; and DNA testing may fail to identify a mutation)
- Answer questions regarding molecular genetic aspects of Fabry disease

Be able to answer general questions relating to potential therapy for Fabry disease, including published trials of enzyme replacement (Refer to the section "Clinical Condition and Medical Management" in the original guideline document).

Be prepared to make appropriate referrals for medical evaluations and further discussions that are beyond the scope of genetic counseling practice (see Figure 1 in the original guideline document).

Provide contact information for support groups as requested (see Table V in the original guideline document).

Follow-up

Arrange/facilitate additional appointments to complete the family history and genetic risk assessment, and arrangements to follow the medical progress of the patient, as indicated.

Devise a plan for disclosing test results.

Offer post testing support counseling (by office visit or telephone).

Facilitate referrals to appropriate professionals, as indicated (see Figure 1 in the original guideline document).

Consider making available to the patient a letter to summarize major topics discussed in the genetic counseling session(s), and to facilitate informing their family members of their genetic risks.

Ethical Issues and Special Considerations

Testing Healthy At-Risk Minors

The age at which to test healthy at-risk minors is controversial, particularly if no therapy or intervention is available, or if it is unknown at what age an intervention should begin for the greatest health benefit for the child. Several position papers and printed discourses raise multiple concerns about potential emotional damage to the child, as well as possible discrimination. Some of the considerations of testing healthy at-risk children for Fabry disease are summarized in Table IV in the original guideline document.

Studies documenting the effect of genetic testing of children at risk for Fabry disease have not been published. Testing of seemingly healthy minors for genetic conditions is usually discouraged, unless testing allows for a health benefit due to medical intervention. Testing for Fabry disease in seemingly healthy at-risk males who are minors may be justified, given the subtle early manifestations of Fabry disease and the high likelihood of disease progression. Early diagnosis allows for closer medical monitoring and the opportunity for early intervention, especially with the prospect of enzyme replacement therapy. Testing healthy at-risk minor females may be more controversial because many female carriers of Fabry disease will never have symptoms. It may be appropriate to time genetic testing for Fabry disease before an adolescent (male or female) becomes sexually active, to assist with discussions of reproductive risks and options.

Testing Siblings Before Kidney Transplant

Before considering a healthy sibling of a person with Fabry disease as an organ donor for the affected male, unaffected status should be confirmed by enzyme analysis or DNA testing. Enzyme analysis or DNA testing should not be initiated solely to secure a matched donor. Female carrier siblings should not be used as organ donors.

Teratogenesis

A careful medication history should be taken for a symptomatic woman who is planning a pregnancy or who is pregnant to determine if any medications she is taking are teratogenic. Dilantin and carbamazepine are commonly used for pain symptoms; their potential teratogenic effects should be reviewed with the client. The patient can be referred to a regional teratogen service for comprehensive information. Listings of such services can be found through the Organization of Teratogen Information Services or OTIS (http://ctispregnancy.org/home.html).

Confirming Parentage

All daughters of affected males with Fabry disease are obligate heterozygotes. Because of possible misattributed paternity, carrier status should not be assumed. Confirmation with enzyme analysis or with DNA testing if the mutation is known is indicated to provide accurate genetic risk assessment and genetic counseling. Enzyme analysis in females may not be definitive, and DNA testing is preferred for diagnostic confirmation; ophthalmologic evaluation may also be useful in establishing carrier status for females (see "Genetic Diagnosis and Genotype/Phenotype Correlations" and Figure 2 in the original guideline document).

CLINICAL ALGORITHM(S)

A suggested diagnostic testing flow-chart for Fabry disease is provided in the original guideline document.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The rating of supporting literature is class III, opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees. No supporting literature for genetic counseling practices in categories I and II was identified. See the "Methods to Assess the Quality and Strength of the Evidence" field of this NGC summary.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate genetic counseling for Fabry disease

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Genetic counseling recommendations of the National Society of Genetic Counselors (NSGC) are meant to assist practitioners in making decisions about appropriate management of genetic concerns. Each practice recommendation focuses on a clinical or practice issue, and is based on a review and analysis of the professional literature. The information and recommendations reflect scientific and clinical knowledge current as of the publication date, and are subject to change as advances in diagnostic techniques, treatments, and psychosocial understanding emerge. In addition, variations in practice, taking into account the needs of the individual patient and the resources and limitations unique to the institution or type of practice, may warrant alternative approaches, treatments, or procedures to the recommendations outlined in this document. Therefore, these recommendations should not be construed as dictating an exclusive course of management, nor does use of such recommendations guarantee a particular outcome. Genetic counseling recommendations are not intended to supersede a health care provider´s best medical judgment. The listing of patient and professional resources does not necessarily imply NSGC endorsement.
- These recommendations should not be construed as dictating an exclusive course of management, nor does use of such recommendations guarantee a particular outcome. The professional judgment of a healthcare provider, familiar with the facts and circumstances of a specific case, will always supersede these recommendations.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Bennett RL, Hart KA, O'Rourke E, Barranger JA, Johnson J, MacDermot KD, Pastores GM, Steiner RD, Thadhani R. Fabry disease in genetic counseling practice: recommendations of the National Society of Genetic Counselors. J Genet Counsel 2002 Apr;11(2):121-46. [51 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 Apr

GUIDELINE DEVELOPER(S)

National Society of Genetic Counselors

SOURCE(S) OF FUNDING

This project was supported by the National Society of Genetic Counselors, Inc. - Medical Specialty Society

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

The authoring subcommittee consisted of experts in genetic counseling, biochemical genetics, clinical/medical genetics, clinical molecular genetics, renal disease, pediatrics, and internal medicine. Input was also sought from a patient advocacy group for Fabry disease.

Subcommittee Members: Robin L. Bennett, Kimberly A. Hart, Erin O'Rourke, John A. Barranger, Jack Johnson, Kay D. MacDermot, Gregory M. Pastores, Robert D. Steiner, Ravi Thadhani

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

This work was initiated by the Fabry International Research Exchange (FIRE) sponsored by Transkaryotic Therapies. Barranger, Bennett, Pastores, Steiner, and Thadhani are paid advisors for FIRE. Barranger, Hart, Steiner, and Pastores receive institutional support from Genzyme Corporation. MacDermot has conducted clinical trials with Transkaryotic Therapies. The Fabry Support and Information Group (FSIG) has received donations from Genzyme Coporation and Transkaryotic Therapies.The authors and reviewers of this paper volunteered their time, and did not receive an honorarium.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Not available at this time.

Print copies: Available from the National Society of Genetic Counselors, 233 Canterbury Drive, Wallingford, PA 19086-7608; Web site: www.nsgc.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Bennett RL, Steinhaus KA, Uhrich SB, et al. Recommendations for standardized human pedigree nomenclature. Am J Hum Genet 1995;56:745-52 and J Genet Couns 1995;4:267-79.

Electronic copies: Not available at this time.

Reprints available from Robin L. Bennett, Medical Genetics, Box 357720, University of Washington Medical Center, Seattle, WA 98195-7720.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on January 9, 2003. The information was verified by the guideline developer on March 11, 2003.

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